Corticosteroiden, kaliumtekort en H-ion-secretie

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SAMENVATTING

De doelstelling van dit proefschrift is weergegeven in de inleiding. Na een bespreking van de relatieve frequentie van maagulcera bij patienten met het syndroom van Cushing en met corticosteroiden behandelde patienten in hoofdstuk I, volgt in hoofdstuk II een beschouwing over de invloed van kaliumdepletie op het vermogen een waterstofion-gradient op te bouwen in de niertubulus en in de maag. De mogelijkheid wordt geopperd, dat het optreden van een maagulcus bij patienten met een 'nonbeta-cell' tumor van de pancreas, afhankelijk is van de mate van kaliumdepletie.

Hoofdstuk III bevat gegevens over de opzet en de uitkomsten van het dier-experimenteel onderzoek.

Hoofdstuk IV beschrijft de bij de mens verkregen uitkomsten. In hoofdstuk V wordt uiteengezet waarom bij dit onderzoek de voorkeur werd gegeven aan de bepaling van de waterstofion-gradient boven de bepaling van de waterstofion-excretie. Vervolgens wordt de relatieve betekenis van kaliumdepletie, al of niet gecombineerd met een overmaat aan mineralocorticoiden of synthetische glucocorticoiden, op het vermogen een waterstofion-gradient op te bouwen, besproken. De conclusie is, dat ook vanuit dit gezichtspunt een terugkeer naar het gebruik van de natuurlijke bijnierschorssteroiden bij de anti-inflammatoire therapie, ongewenst is.

SUMMARY

This thesis describes the influence of various conditions on hydrogen ion-secretion by the renal tubule and the gastric mucosa. Gastric and duodenal ulcer, frequently observed in iatrogenic Cushing's syndrome, is only rarely encountered in the natural disease. On the contrary in primary aldosteronism, a disease characterized by hypokalemia and mineralocorticoid excess, a diminished gastric acid secretion is seen.

This led us to the question whether the absence of mineralocorticoid excess and thus the absence of potassium depletion in iatrogenic Cushing's syndrome are possibly responsible for the higher incidence of gastric ulcer. Natural Cushing's syndrome, by definition exhibiting mineralocorticoid excess and more or less potassium depletion, would then be protected by this mechanism. Of course it is well recognized that gastric secretion of hydrochloric acid itself needs not be the causative agent in ulcerogenesis. On the other hand all conservative or surgical therapeutic measures are meant to diminish hydrochloric acid secretion and they are usually successfull. If interference of potassium depletion and mineralocorticoid excess on hydrogen ion-secretion is a general metabolic principle then it should be demonstrable in other tissues capable of secretion of acid, notably the renal tubule.

In table 1 the literature data on ulcer formation in iatrogenic Cushing's syndrome are summarized. Unfortunately equivalent series of natural Cushing's syndrome are not available, but it is of some interest that in the large series of Plotz and of Hurxtal and Soffer no mention of gastric symptoms has been made whereas at autopsy of these patients an ulcer is very seldom seen.

Potassium depletion in patients is caused by deficient intake, by emesis, diarrhoea or renal loss. Apart from intake the magnitude of the urinary potassium excretion is determined by the degree in which it is actively reabsorbed in the proximal tubule and secreted in the distal tubule. According to Berliner and Orloff sodium is exchanged for

potassium and hydrogen ions in the distal tubule whereas the secretion of potassium is inversely related to that of hydrogen ions. The whole nephron secretes hydrogen ions as shown by Gottschalk and Bloomer.

The two clinical conditions in which chronic potassium depletion most commonly occurs are anorexia nervosa and primary aldosteronism. In addition it is often encountered after administration of thiazide compounds and, much less often, in the rare syndrome of non-beta-cell tumour of the pancreas. Apparently two clinical forms of this syndrome exist, one with severe potassium depletion and diarrhoea, the other with gastric hypersecretion and recurrent ulcers. The literature concerning this syndrome is summarized in table II. It is remarkable that ulcer formation and hyperacidity are mainly found in patients without potassium depletion and it is tempting to speculate that the clinical picture is dependant on the degree of potassium depletion.

Experimentally the production of potassium depletion combined with mineralocorticoid excess diminishes the hydrochloric acid secretion in the gastric mucosa in the rat. On the other hand administration of prednisone gives an increase of hydrochloric acid production in this animal but this has not been found in man.

In order to study the relative importance of potassium depletion alone or in combination with an altered hormonal environment on gastric acid secretion, six groups of rats were studied. Rats varying in weight from 200 to 260 grams were used. The rats were prepared either with a potassium deficient diet, with and without DOCA, or a diet with added potassium with DOCA or a normal diet combined with prednisolone. The influence of potassium depletion combined with administration of prednisolone was also studied. The composition of the experimental diet shown in table IV is the same as that given by Irvine. Potassium depletion was obtained by addition of 500 grams Resonium A to the diet instead of the potassiumdiphosphate. The rats were maintained on the different diets for four weeks before actual experiments were carried out. In table III the data concerning the various groups and the hormones supplied with the diet are summarized. The administration of pharmaca was not corrected for weight. Gastric fluid was collected four hours after tying off the pylorus and injecting 2 mg of histaminediphosphate. In the experiments in which the acidification of urine was studied, 50 mg of ammoniumchloride was given intra-peritoneally and the urine was collected under liquid paraffin with added toluol. Blood was obtained by cardiac puncture at

the end of both experiments for the determination of pH and standard bicarbonate.

The effects of the various experimental conditions on the parameters studied in blood, gastric fluid and urine will be discussed in this order. The serum potassium falls on a potassium deficient diet as is to be expected. If DOCA is given in addition a more pronounced fall in serum potassium occurs. These data are given in table V and figure 1. When the normal diet, containing sodium chloride, with added potassium is given combined with DOCA, the serum potassium is higher than on a potassium deficient diet combined with DOCA (table V, figure 1).

A potassium deficient diet results in a higher pH and standard bicarbonate content of the blood, also when DOCA or prednisolone are given in addition. This rise does not occur when potassium is added to the diet together with DOCA (table VI, figure 2). Under all experimental conditions administration of ammoniumchloride gave a measurable fall of pH and standard bicarbonate as shown in figures 2 and 3.

Table VIII and figure 6 demonstrate the effect of the different dietary regimes on pH and volume of the gastric fluid. A potassium deficient diet induces a marked rise of the pH and a fall of the volume. Administration of DOCA intensifies this effect. Administration of prednisolone leads to a diminished volume of gastric fluid. When prednisolone is given combined with a diet with normal potassium content the pH of gastric fluid falls while its volume rises. Administration of DOCA and potassium supplements results in a lower pH than a potassium deficient diet with DOCA.

The effects of the different dietary regimes on urine pH are given in table IX and figure 7. A potassium deficient diet with and without added DOCA results in a higher urinary pH as compared to normal conditions. Administration of prednisolone during potassium depletion results in a higher pH than in a control group. When a diet with potassium supplements together with DOCA is given the urinary pH is found to be lower than during potassium depletion and DOCA administration. Prednisolone given with a normal diet results in a higher urinary pH than in the control group. This is in apparent contrast with the findings in gastric fluid under the same conditions. Wrong has described that urinary flow during an ammonium chloride acidification test has an effect to some degree on the lowering of pH in man. Perhaps this mechanism may account for the discrepancy in the

findings in gastric fluid and urine in the rat, though it should be noted that diuresis was by no means excessive in all cases.

Urinary acidification and gastric secretion of hydrochloric acid were studied clinically in six patients on prednis(ol)one medication and in six other patients. All had disorders not known to be associated with gastric or renal disease. Their clinical diagnosis and dosage and duration of steroid therapy are given in tables IX and X. Patients with a pulmonary disorder had sufficient arterial oxygenation. There was no manifest disturbance of carbohydrate tolerance. Gastric acid was collected after 30, 60, 75, 105 and 120 minutes. Following collection of the second sample 0.04 mg histaminediphosphate per kg bodyweight was given i.m. preceded by 25 mg promethazin. In the acidification test of the urine, Wrong's procedure, with a slight modification, was followed. Urine was collected every hour. Six grams of ammoniumchloride was given orally one hour after the start of the studies.

The effect of the experimental procedures on blood, gastric fluid and urine will also be discussed in this order. Administration of ammonium chloride resulted in a fall in pH and standard bicarbonate as expected and shown in figure 9. Figure 8 gives blood pH and standard bicarbonate following the histamine injections. Administration of prednis(ol)one gave a lower pH of the gastric fluid prior to histamine administration when compared with a control group. Following histamine no difference was found between the two groups. These data are given in tables XII and XIII and figure 10.

The data on the urinary acidification test in the patients on prednis(ol)one medication are given in table XV and figure 12, the data on the controls in table XIV and figure 11. Administration of prednisolone has no demonstrable effect on the renal ability to lower urinary pH. The difference in diuresis between the control- and the prednis(ol)one group might be attributable to a difference in fluid intake since this was not standardized. Nevertheless diuresis in the prednis(ol)one group was not important enough to obscure a possible effect of this medication on urinary pH. According to Wrong this is only the case when diuresis exceeds 8 ml per minute.

The effect of potassium depletion under clinical circumstances was studied in three patients with primary aldosteronism and two patients with anorexia nervosa. In all instances complete endocrine studies were done before arriving at the diagnosis. Two patients were operated upon successfully, the third died of adrenal carcinoma with metastases. For the results the reader is referred to tables XVI, XVIII, XIX,

xx and xxii. One patient with primary aldosteronism and one with anorexia nervosa were studied after successfull treatment. The results of repeated tests in these patients are given in tables xvii and xxi.

It appears that the ability to establish a hydrogen ion-gradient in the renal tubule and gastric mucosa is less in all patients when compared with the earlier mentioned control group. Successfull treatment resulted in normalization of these functions in the two patients restudied. In the clinical studies the Na/K ratio is given of both gastric fluid and urine under the different experimental circumstances. In no instance was a correlation observed between Na/K ratio and pH.

A few words should be added to explain why urinary and gastric pH were studied rather than hydrogen ion-clearance and total gastric acid secretion in our experimental and clinical studies. According to Elkinton the hydrogen ion-clearance is calculated from the total of titrable acid and ammonia excreted after subtracting urinary bicarbonate, using serum CO_2 as a measure for the hydrogen ion-content of blood. It has been shown by Pitts and Sullivan that the diffusion of ammonia in the renal tubule is a passive process while the excretion of ammonia is related to glomerular filtration. Therefore the renal hydrogen ion-clearance cannot be considered to be an adequate index of the ability of the renal tubule to establish a hydrogen ion-gradient. When studying gastric ability to secrete hydrogen ion no marring of the picture by ammonia occurs but here the difficulty to obtain complete samples of gastric fluid makes it impossible to measure total gastric acid secretion accurately.

In conclusion it was shown that potassium depletion alone or in combination with mineralocorticoid excess does indeed diminish renal and gastric ability to establish a hydrogen ion-gradient both in patients and in the animal experiments. However this effect is seen only when potassium depletion is present in a severe degree. It is therefore not indicated to return to the old treatment with cortisone and hydrocortisone in conditions where antiinflammatory treatment is intended, with the intention of possibly protecting against gastric ulcer.